Synthesis of 1,2-Azaphosphetidines

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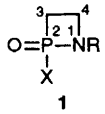
Photolytic or rhodium catalysed decomposition of α-diazo-β-ketophosphonamidates and intramolecular C–H insertion of the resulting carbene intermediates is the key step in the synthesis of mono and bicyclic 1,2-azaphosphetidines.

Very few 1,2-azaphosphetidines are known in spite of the great interest attached to their 2-oxo derivatives **1** as close structural analogues of azetidinones (β-lactams) **2**, though several β-sultam analogues **3** have been reported.[1] 1,2-Azaphosphetidines were first reported by Gubnitskaya and coworkers from an intramolecular Arbuzov reaction,[2] and recently Bertrand and coworkers produced a further example by the thermal decomposition of a bisphosphanyldiazomethane.[3] We now report a general route to the ring system in which the last step is a carbene mediated C-3–C-4 ring closure.

Photolytic or catalysed decomposition of the α-diazo-β-ketophosphonamidates **4** gave a carbene or carbenoid which underwent Wolff rearrangement and C–H insertion to give the four-membered ring as the two major reaction pathways (Scheme 1). The β-ketophosphonamidates **5–10** (Table 1) were prepared by the Arbuzov reaction between phenacyl bromide and diethyl phosphorus amides, generated *in situ* from diethyl chlorophosphite and a secondary amine, as outlined in Scheme 2. The Arbuzov reaction yields were often rather low because of an accompanying Perkov reaction (Scheme 2). Diazo transfer to the active methylene group to form compounds **11–16** always proceeded in high yield. The



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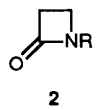

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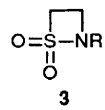

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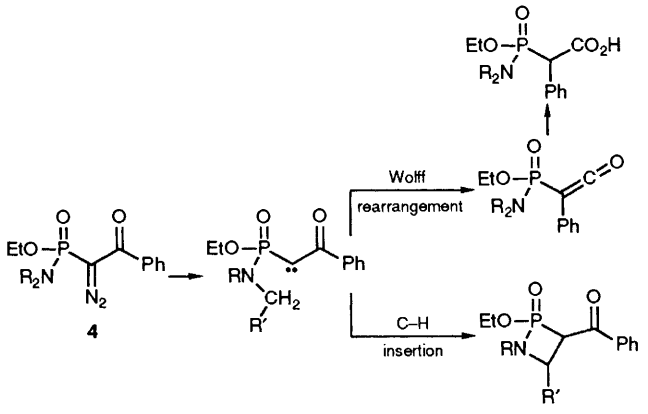
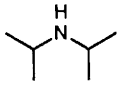
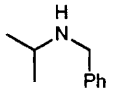
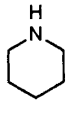
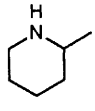
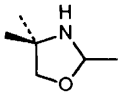


Scheme 1

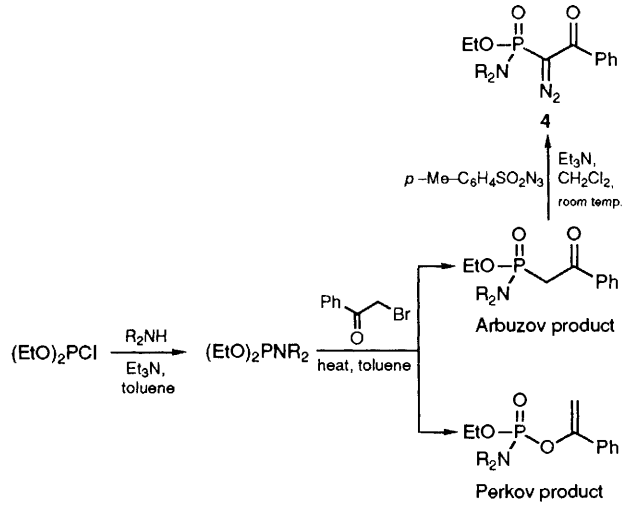
Table 1 Synthesis of β-ketophosphonamidates and α-diazo-β-ketophosphonamidates

R_2NH	EtO–P(O)(NR₂)–CH₂–C(O)–Ph		EtO–P(O)(NR₂)–C(N₂)–C(O)–Ph	
	**5**	67%	**11**	98%
	**6**	50%	**12**	87%
	**7**	53%	**13**	100%
	**8**	24%	**14**	75%
	**9**	22%	**15**	80%
	**10**	36%	**16 a,b**	96%

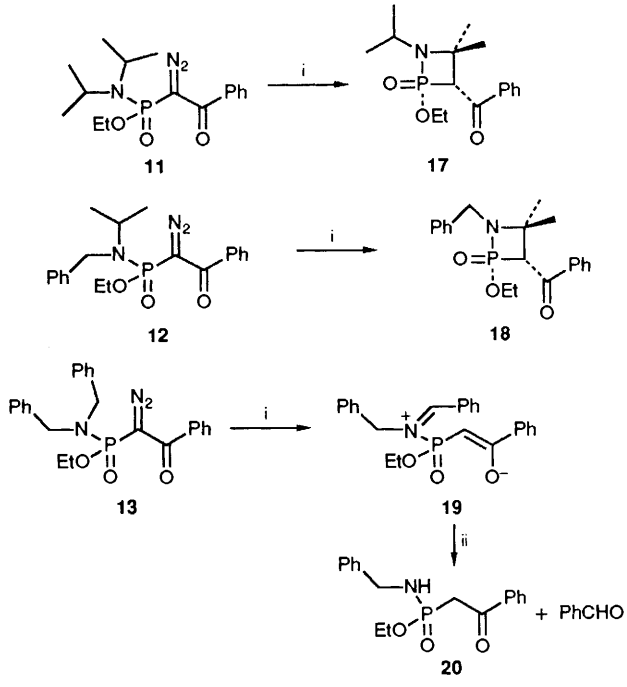
two diastereoisomers of compound **16** were separated chromatographically and their relative stereochemistry assigned from NOE experiments.

The diisopropylamino compound **11** decomposed smoothly with rhodium acetate catalysis in refluxing 1,2-dichloroethane for 3 h to give the insertion product **17**† in 33% isolated yield.

† *Spectroscopic data*: ν_{max}/cm^{-1} (KBr disc) 2974, 2931, 2878, 1682 (C=O), 1598, 1449, 1391, 1370, 1273, 1241 (P=O), 1208, 1161, 1130, 1030, 997, 944, 758, 692, 647, 580 and 522; δ_H (270 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7 Hz, Me of OEt), 1.28 (3H, d, *J* 6.6 Hz, Me of Pr^i), 1.29 (3H, d, *J* 6.6 Hz, Me of Pr^i), 1.53 (6H, s, 2 × 4-Me), 3.26 (1H, dheptet, J_P 20 and J_H 6.6 Hz, $CHMe_2$), 3.68–3.77 and 3.90–4.03 (2H, m, CH_2O) 4.44 (1H, d, J_P 23 Hz, 3-H), 7.46–7.61 (3H, m, aromatic H) and 8.02–8.04 (2H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 19.2; m/z (70 eV), 140 °C) 309 (M^+, 6), 294 ($M^+ - Me$, 79), 105 ($PhCO^+$, 73), 84 (57), 77 (Ph, 39), 44 [$(Pr^i + H)^+$, 100], 42 [$(Pr^i - H)^+$, 92] and 41 (31).



Scheme 2



Scheme 3 *Conditions*: i, $Rh_2(OAc)_4$, $ClCH_2CH_2Cl$, reflux, 3 h; ii, H_2O (work-up)

Under the same conditions the benzylisopropylamino compound **12** gave only a 16% yield of the analogous product **18**, and the dibenzylamino compound **13** gave a complex reaction mixture from which only the monobenzylamide **20** (12%) could be isolated, though benzaldehyde was detected. These results show that insertion into a benzylic C–H bond is much less favoured than into an isopropyl tertiary C–H; this is possibly because in the former, hydride abstraction by the carbene supervenes to give a more stabilised intermediate **19** which does not collapse to the four-membered ring (Scheme 3).

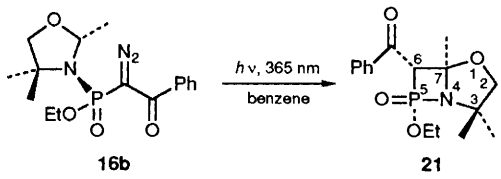
Both insertion products, **17** and **18**, were formed diastereoselectively,‡ in a ratio of about 10 : 1 in favour of the (S_P, R_C) relative configuration. The relative stereochemistry of **17** was established by X-ray crystallography, which also confirmed the structure of the compound.[4] The four-membered ring is buckled by 8° from planarity, the nitrogen atom is

‡ Diastereoisomeric ratios were determined from ^{31}P NMR.

trigonal, and the bulky groups on P-2 (ethoxy) and C-3 (benzoyl) are *cis*. This striking stereoselectivity could be explained if the α-diazophosphonamidate has the same (*cisoid*) conformation as that established for α-diazoketones,[5] and if this conformation is preserved in the cyclisation process. The dominance of *cisoid* isomers in α-diazoketones has been rationalised in terms of an attractive interaction between the C=O and $C=N_2$ dipoles,[5] and it is possible that a similar, though stronger, interaction between P=O and $C=N_2$ would favour a similar pre-insertion conformation here.

We next attempted the analogous synthesis of fused bicyclic azaphosphetidines from diazo compounds **14, 15** and **16a** and **b**. With all of these the proportion of Wolff rearrangement product was higher, presumably because of increased strain associated with the bicyclic transition state for the insertion reaction. Thus, decomposition of **14** and **15** gave only the corresponding Wolff rearrangement products [50% (*hν*), 64% (Rh^{2+}) and 50% (*hν*), 34% (Rh^{2+}), respectively] and similarly no C–H insertion was observed with the *cis* diastereoisomer **16a**. However, photolysis of the *trans* diastereoisomer **16b** gave a 4 : 1 diastereoisomeric mixture of the bicyclic azaphosphetidine **21**§ (Scheme 4) in low yield (13%).

Thus, a short synthesis of β-ketophosphonamidates and



16b **21**

Scheme 4

decomposition of their α-diazo derivatives provides a ready synthetic approach to 2-oxa-1,2-azaphosphetidines.

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4 D. J. Williams, Chemistry Department, Imperial College, unpublished results.
5 S. Sorriso, in *The Chemistry of Diazonium and Diazo Groups*, ed. S. Patai, Wiley, Chichester, 1978, pp. 113–123.

§ *Spectroscopic data*: ν_{max}/cm^{-1} (CH_2Cl_2) 2977, 1682 (C=O), 1598, 1581, 1449, 1392, 1372, 1286, 1196 (P=O), 1163, 1107, 1021, 908, 822, 776, 690, 631, 518 and 504; δ_H (500 MHz, $CDCl_3$), (* refers to the distinguishable signal of the minor diastereoisomer) 1.18 (6H, s, Me_2C, 1.20 (3H, t, *J* 7 Hz, ester Me), 1.42 and 1.40* (3H, s, 7-Me), 3.68* and 3.95 (2H, m, ester CH_2O), 4.09 and 4.06* (1H, dd J_P 17 and J_H 11 Hz, 2-H), 4.22 and 4.44* (1H, dd, J_P 2 and J_H 11 Hz, 2-H), 5.25* and 5.29 (1H, d, J_P 13 Hz, 6-H), 7.49 (2H, t, *J* 7 Hz, aromatic H), 7.60 (1H, t, *J* 7 Hz, aromatic H), 8.00* and 8.14 (2H, d, *J* 7 Hz, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 3.78 (80%) and 9.06* (20%); *m/z* (70 eV, 150 °C) 323 (M^+, 1), 297 (12), 192 (76), 149 (15), 105 (100), 82 (15), 77 (27), 56 (10) and 55 (14).